

305,509

1090797

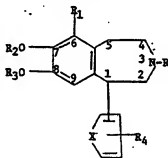
DEC-2 1980

ABSTRACT OF THE DISCLOSURE

A group of 7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzoserpine with structures containing a thienyl or furyl ring at position 1 which have dopaminergic activity. Particular species of this group include 7,8-dihydroxy-1-(3'-methoxy-2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzoserpine and its dimethyl ether derivative, 7,8-dihydroxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzoserpine and its dimethyl ether as well as 7,8-dihydroxy-1-(3'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzoserpine and its dimethyl ether and 7,8-dimethoxy-3-methyl-1-(3'-methoxy-2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzoserpine.

This invention comprises a new group of compounds which have structures characterized by being 1-thienyl and 1-furyl-2,3,4,5-tetrahydro-1H-3-benzazepines having two hydroxy substituents in the benz-ring of the benzazepine nucleus. These new compounds have utility as medicinally active compounds especially as cardiovascular agents due to their peripheral dopaminergic activity. They also demonstrate activity in animal tests which are known to predict anti-Parkinsonism activity by means of activity at the central dopamine receptors. Generally speaking therefore they may have both peripheral or central dopaminergic activity.

The structures of the compounds of this invention are specifically identified by having a thienyl or furyl hetero ring at the 1-position of the 2,3,4,5-tetrahydro-1H-3-benzazepine system. Exemplary of this new group of compounds are those represented by the following structural formulas:



in which:

R is hydrogen, phenethyl, benzyl, lower alkanoyl of from 1-5 carbons such as formyl, acetyl or trifluoroacetyl, lower alkyl of 1-5 carbon atoms, hydroxyethyl or lower alkenyl of 3-5 carbon atoms;

R<sub>1</sub> is hydrogen, halo, trifluoromethyl, lower alkylthio such as methylthio or ethylthio, trifluoromethylthio, methyl or methoxy;

1  $R_2$  and  $R_3$  are each hydrogen, lower alkyl of 1-5 carbon  
atoms, lower alkanoyl of 2-5 carbon atoms or, when taken  
together, methylene or ethylene;

5  $R_4$  is hydrogen, halo such as F, Cl or Br, cyanomethyl,  
carbomethoxy or methyl and

X is -O- or -S- .

In the above structural formulas those skilled in the art  
will recognize that the hetero ring is attached at its 2' (a) or  
3' (b) position. The substituents on the two hetero rings are merely  
10 limited by the constraints of furan or thiophene chemistry but are of  
course C-attached.

The thienyl containing congeners are preferred. The furyl  
congeners may be less active and more toxic than their thienyl counter-  
parts.

15 A subgeneric group of compounds within the above illustrative  
generic group are those of Formula I in which:

R is hydrogen or methyl;

$R_1$  is hydrogen or chloro;

$R_2$  and  $R_3$  are the same and are hydrogen, methyl

or acetyl;

20  $R_4$  is hydrogen or methyl; and

X is -S- .

The compounds of this invention may also have a fourth benz  
substituent such as at the 9 position but these have not yet been shown  
to have any particular advantage from the viewpoint of their biological  
25 utility. The compounds in which  $R_2$  and  $R_3$  are higher alkyl or alkanoyl  
groups or form an alkylene chain such as the methylenedioxy-containing  
compounds at the 7,8-positions as well as the N-benzyl, phenethyl or  
alkanoyl containing congeners are of primary interest as intermediates.  
Methylenedioxy-3-benzazepines in another series are reported in U.S.  
30 Patent 3,795,683.

1           The pharmaceutically acceptable acid addition salts having  
the utility of the free bases of formula I, prepared by methods well  
known to the art, are formed with both inorganic or organic acids, for  
example: maleic, fumaric, benzoic, ascorbic, pantoic, succinic,  
5   bismethylene-salicylic, methanesulfonic, ethanedithiosulfonic, acetic,  
oxalic, propionic, tartaric, salicylic, citric, gluconic, aspartic,  
stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic,  
benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexyl-  
sulfamic, phosphoric and nitric acids. Similarly the quaternary  
10   salts include those prepared from organic halides such as methyl  
iodide, ethyl iodide or benzyl chloride, methyl tosylate or mesylate  
which react at the basic 3-center or at a reactive thio center. While  
the 1-furylbenzazepines form salts readily with strong mineral acids  
such as sulfuric or hydrochloric acid, such salts are less stable and  
15   hard to purify. Therefore the furyl containing compounds are best  
used either as the base or as a salt with an organic or weak inorganic  
acid.

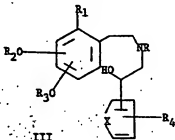
Certain 1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepines have  
been described in U.S. Patent 3,393,192; British Patent Specification  
1,118,688; and Swiss Patent 555,831, including general methods of  
20   preparation. However these references disclose no 1-heterosubstituted  
compounds.

It will be obvious to one skilled in the art that the compounds  
of Formula I may be present as diastereoisomers which may be resolved  
into d or l optical isomers. Resolution of the optical isomers may be  
25   conveniently accomplished by fractional crystallization of the salts  
of the base form or of solid derivatives thereof with optically active  
acids from appropriate solvents. Unless otherwise specified herein or  
in the claims, it is intended to include all isomers, whether separated  
or mixtures thereof. Where isomers are separated, the desired  
30   pharmacological activity will usually predominate in one of the isomers,

1 most often in the d-isomer.

The compounds of Formula I in which R is hydrogen are generally prepared from intermediates of the following formula:

5



10 in which R is hydrogen, lower alkyl, benzyl or lower alkenyl;  $R_1$  and X are as defined above;  $R_2$  and  $R_3$  are lower alkyl or together are lower alkylene; and  $R_4$  is hydrogen or a chemically inert substituent of the group described above, by means of an intramolecular cyclization effected by reaction with a reagent such as

15 sulfuric acid alone or mixed with suitable solvents such as trifluoroacetic acid, polyphosphoric acid or a similar dehydrating agent.

Mixed alkoxy substituted compounds are prepared by selecting the proper heteroarylethylamine starting material.

20 The cyclization is best run to form the methylenedioxy or dimethoxy ethers, then these ether groups are optionally taken off using a mild splitting agent such as boron trichloride for the methylenedioxy or tribromide for the dimethoxy ether.

The heteroarylethylamines (IV) which are used as starting materials for this method are either known or are prepared by methods

25 similar to those disclosed in the illustrative examples.

30

1           The 6-substituted compounds are alternatively prepared by  
oxidizing a 7,8-dihydroxy-1-(furyl or thienyl)-2,3,4,5-tetrahydro-1H-  
3-benzazepine with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or similar  
5   hydroquinone-oxidizing agent to form the 7,8-dione. This is then  
reacted with a quinone additive agent, a nucleophilic reagent, such as  
methyl mercaptan, trifluoromethyl mercaptan, hydrogen chloride or  
hydrogen bromide (in the case where no acid sensitive centers are  
present) in methanol at about room temperature to give the desired  
6-substituted compound.

10           The 6-bromo containing compound may optionally serve as an  
intermediate in a number of ways such as for preparing the 6-chloro  
or 6-iodo congeners or the 6-lithium intermediates. The latter  
lithium compounds can be reacted with a number of other conventional  
reactants to introduce 6-substituents such as with iodine or  
15   hexachloroethane to introduce iodo or chloro.

          To prepare the compounds of Formula I where R is hydroxyethyl,  
lower alkyl or lower alkenyl, the corresponding benzazepines wherein R  
is hydrogen are alkylated by standard methods with ethylene oxide, a  
reactive lower alkyl halide such as the bromide or chloride or a  
reactive alkenyl halide such as an allyl bromide or chloride.  
20   Advantageously, to obtain the products where R<sub>2</sub> and/or R<sub>3</sub> are hydrogen  
the reaction with the alkylating agent is carried out on the corres-  
ponding methoxy substituted benzazepines in an inert solvent such as  
methanol or acetone, preferably at reflux temperature and in the  
presence of a basic condensing agent such as potassium hydroxide or  
25   carbonate. Treatment of the resulting product with, for example  
boron tribromide or other ether splitting agents gives the active  
hydroxy substituted benzazepines. If a reactive center such as a  
methylthio group is present the sulfonium quaternary salt is  
prepared. This may be optionally converted back to the methylthio  
30

1 by heating in brine, 1N hydrobromic acid or another source of halide ions. The 3-methyl congeners are an important part of this invention.

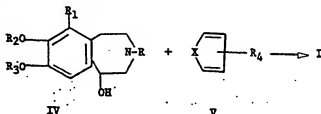
5 The compounds of Formula I where R is methyl are conveniently prepared from 7,8-dimethoxy substituted benzazepines wherein R is hydrogen by reaction with formic acid/formaldehyde. Treatment of the resulting product with boron tribromide gives the corresponding 7,8-dihydroxy substituted benzazepines. Another method for preparing the important N-methyl compounds is converting the 3-hydrogen compound into the N-formyl congener then reducing with lithium aluminum hydride, 10 a two step reaction sequence.

15 The dialkanoyloxy derivatives such as the important 7,8-diacetoxy compounds can also be prepared by direct O-acylation of the dihydroxy compound having the N-position blocked by protonation such as using the 6-halo-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide in trifluoroacetic acid at ambient temperature with the anhydride or halide. The N or 3-lower alkanoyl congeners in the dihydroxy series are prepared conveniently by N-acylating the methoxy or methylenedioxy derivative followed by splitting the protective group with boron tribromide or chloride. Also direct N- 20 alkanoylation of the dihydroxy compounds is possible under controlled conditions and quantities of reactants as known to the art. As noted in the illustrative examples any undesired O-acylation may necessitate a mild hydrolysis treatment.

25 The intermediates of Formula III above are conveniently prepared by heating equimolar amounts of an epoxyethylthiophene or furan with a 3,4-dialkoxyphenethylamine which is either known or prepared by methods known to the art, each appropriately substituted, either alone or in an inert organic solvent such as tetrahydrofuran. Preferably the heating is effected on a steam bath or at reflux 30 temperature for from 12 to 24 hours. The required ethylene oxide is

conveniently prepared by reaction of the hetero aldehyde with sodium hydride/trimethylsulfonium iodide.

The compounds of this invention can also be conveniently prepared by a process we believe is unique in the benzazepine series as illustrated by the following:



The 1-hydroxy-2,3,4,5-tetrahydro-1H-3-benzazepines of Formula IV are reacted with compounds (V) in which R-R<sub>4</sub> and X are as defined above. As one skilled in the art will recognize certain compounds such as thiophene will react at the position adjacent to the hetero ring member unless that position is occupied. For example the method works nicely to prepare 2'-thienyl compounds. The reaction can also be run to obtain mixtures of mono and poly substituted products which can be separated by methods known to the art. If one or both the α-positions on the heterocycle are occupied, reaction proceeds either in the remaining α or on to the β-position.

The reaction can also be run using IV and in place of a heterocyclic V using benzene having activating groups such as phenol or anisole to produce substituted 1-phenylbenzazepines. R-R<sub>4</sub> are as defined above but for convenience the reaction is usually run on the 1-hydroxybenzazepines in the form of the diether (for example, R<sub>2</sub>, R<sub>3</sub> = methyl or, together, methylene) with or without the N or 3-position protected such as N-protective groups known to the art, for example benzyl or carbobenzoxy to prepare the 3-hydrogen compounds.



1           The reaction is run at ambient temperature such as at  
room temperature for convenient periods of time such as from 1-24  
hours. Overnight at room temperature is a convenient laboratory  
time period. The solvent may be any inert organic solvent or an  
5   excess of an organic acid solvent in which the reactants are  
soluble for example trifluoroacetic acid, methylene chloride,  
trichloroethylene, chloroform or carbon tetrachloride. Also at  
least one equivalent of acid catalyst must be present such as  
trifluoroacetic acid, sulfuric acid, boron trifluoroetherate, etc.  
10   Certain 1-hydroxy or alkoxy benzazepines are known to the art such  
as G. Hazebroucq, Compt. Rend. 257, 923 (1963) [C.A. 59, 12759] or  
J. Likforman, Compt. Rend. 268, 2340 (1969) [C.A. 71, 61184]. However,  
the specific 1-hydroxy-7,8-dihydroxy-benzazepine starting materials  
used here are new and are prepared by methods disclosed in the  
15   examples.

          The active dopaminergic compounds of this invention used  
herein stimulate peripheral dopamine receptors, for example they  
increase renal blood flow and have as an end result hypotensive  
activity. This renal vasodilator activity of the benzazepine compounds  
20   of Formula I is measured in an anesthetized dog. In this phar-  
macological procedure, a test compound is administered at progressively  
increasing (3-fold) infusion rates beginning at 0.1 mcg/kg/min up to  
810 mcg/kg/min for 5 minutes each to anesthetized normotensive dogs  
and the following parameters are measured: renal artery blood flow,  
iliac artery blood flow, arterial blood pressure and heart rate.  
25   Results are reported as a percent change, increase or decrease, at  
time of peak response (from pre-drug controls), and for a significant  
effect renal blood flow (increase) and renal vascular resistance  
(decrease) should be approximately 10% or greater. The effect on renal  
30   vascular resistance can be calculated from any change in renal blood

1 flow and arterial blood pressure. To confirm the mechanism of  
 action, representative active renal vasodilator compounds are  
 checked for blockade by bulbo-capnine which is known to be a  
 specific blocker of renal dopamine receptors. Representative  
 5 of compounds of Formula I for example: 7,8-dihydroxy-1-  
 (2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide  
 tested by i.v. infusion as described above produced a decrease  
 of renal vascular resistance of 30% at 30 mcg/kg; 7,8-dimethoxy-  
 1-(5'-methyl-2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine  
 10 hydrochloride had an  $ED_{15}$  of 2.3 mcg/kg; 7,8-dihydroxy-1-(3'-  
 thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide had an  
 $ED_{15}$  of 40; the 5-methyl-2-thienyl, 50.  $ED_{15}$  therefore is the  
 cumulative dose by infusion which produces a 15% decrease in renal  
 vascular resistance ( $R = \frac{B.P. \text{ in mm/hg}}{B.F. \text{ ml/min}}$ ).

15 In addition to the renal vasodilator activity via a  
 dopaminergic effect, certain benzazepine compounds of Formula I have  
 demonstrated weak diuretic activity. Such diuretic activity is  
 measured in the standard saline-loaded rat procedure. A test compound  
 is administered i.p. at doses of from 10 to 40 mg/kg and the parameters  
 20 measured are urine volume (hourly for three hours) plus sodium and  
 potassium ion concentrations. Also conventional diuretic tests in the  
 dog may be used. 7,8-Dihydroxy-1-(2-thienyl)-2,3,4,5-tetrahydro-1H-  
 3-benzazepine hydrobromide tested in the phosphate mannitol dog produced  
 a significant increase in renal plasma flow and natriuresis at a dose  
 25 as low as 10 and 20  $\mu\text{g/kg/min}$  i.v. Similar results were obtained at  
 oral doses of 20 mg/kg.

The benzazepine compounds of Formula I also have some anti-  
 parkinsonism activity due to central dopaminergic activity as demon-  
 strated by employing a modified standard animal pharmacological test  
 procedure reported by Ungerstedt et al., in Brain Research 24, 1970,

1 485-493. This procedure is based on a drug induced rotation of  
rats having extensive unilateral lesions of the substantia nigra.  
Briefly, the test comprises the quantitative recording of  
rotational behavior in rats in which 6-hydroxydopamine lesions of  
5 the nigrostriatal dopamine system have been produced. A unilateral  
brain lesion in the left substantia nigra causes the dopamine  
receptor in the left caudate to become hypersensitive following  
the resulting degeneration of the nigral cell bodies. These lesions  
destroy the source of the neurotransmitter dopamine in the caudate  
10 but leave the caudate cell bodies and their dopamine receptors intact.  
Activation of these receptors by drugs which produce contralateral  
rotation, with respect to the lesioned side of the brain, is used as  
a measure of central dopaminergic activity of the drug.

Compounds which are known to be clinically effective in  
15 controlling parkinsonism, such as, for example, L-dopa and apomorphine,  
are also effective in the rate turning model. These compounds directly  
activate the dopamine receptors and cause contralateral rotation of the  
lesioned rat.

Rotational activity is defined as the ability of a compound  
20 to produce 500 contralateral rotations during a two-hour period after  
administration, usually intraperitoneally. The dose corresponding to  
500 contralateral rotations per two hours is obtained and assigned as the  
RD<sub>500</sub> value.

Once again representative compounds of Formula I, 7,8-dihydroxy-  
25 1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide, the  
3'-thienyl and the 5'-methyl-3'-thienyl congeners when tested as described  
above in rats produced activity, i.p. at 5.5 (ED<sub>500</sub>), 5 (active) and  
1.5 (ED<sub>500</sub>) mg/kg respectively. Further the compounds have a low  
potential for inducing emesis or stereotyped behavior at doses which are  
effective in the rat turning model.  
30

1           The pharmaceutical compositions of this invention having  
dopaminergic activity are prepared in conventional dosage unit forms  
by incorporating a compound of Formula I, an isomer or a pharmaceutically  
acceptable addition of salt thereof, with a nontoxic pharmaceutical  
5           carrier according to accepted procedures in a nontoxic amount sufficient  
to produce the desired pharmacodynamic activity in a subject, animal or  
human. Preferably the compositions will contain the active ingredient  
in an active but nontoxic amount selected from about 25 mg to about  
500 mg of active ingredient per dosage unit but this quantity depends  
10           on the specific biological activity desired and the conditions of  
patient. Generally speaking lower doses are needed to stimulate central  
dopamine receptors than peripheral receptors. The dosage units are  
given from 1-5 times daily.

          The pharmaceutical carrier employed may be, for example,  
15           either a solid or liquid. Exemplary of solid carriers are lactose,  
terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium  
stearate, stearic acid, and the like. Exemplary of liquid carriers  
are syrup, peanut oil, olive oil, water and the like. Similarly the  
carrier or diluent may include any time delay material well known to  
20           the art, such as glyceryl monostearate or glyceryl distearate alone  
or with a wax.

          A wide variety of pharmaceutical forms can be employed.  
Thus, if a solid carrier for oral administration is used the  
preparation can be tableted, placed in a hard gelatin capsule in  
powder or pellet form, or in the form of a troche or lozenge. The  
25           amount of solid carrier will vary widely but preferably will be  
from about 25 mg to about 1 g. If a liquid carrier is used, the  
preparation will be in the form of a syrup, emulsion, soft gelatin  
capsule, sterile injectable liquid such as an ampul, or an aqueous  
30           or nonaqueous liquid suspension.

1           The pharmaceutical preparations are made following the  
conventional techniques of the pharmaceutical chemist involving  
mixing, granulating and compressing when necessary, or variously  
mixing and dissolving the ingredients as appropriate to give the  
5       desired end product.

          The method of producing dopaminergic activity in accordance  
with this invention comprises administering internally to a subject  
in need of such activity a compound of Formula I or a pharmaceutically  
acceptable acid addition salt thereof, usually combined with a  
10      pharmaceutical carrier, in a nontoxic amount sufficient to produce  
said activity as described above. The route of administration may be  
any route which effectively transports the active compound to the  
dopamine receptors which are to be stimulated such as orally or  
parenterally, the oral route being preferred. Advantageously, equal  
15      doses will be administered several times such as two or three times  
a day with the daily dosage regimen being selected from about 50 mg  
to about 2 g. When the method described above is carried out hypo-  
tensive, diuretic or antiparkinsonism activity is produced with a  
minimum of side effects.

20           The following examples are designed solely to illustrate  
the preparation and use of the compounds of this invention. The  
temperatures are Centigrade. Other variations of these examples will  
be obvious to those skilled in the art.

EXAMPLE 1

25           4.84 Grams of sodium hydride (57% of mineral oil dispersion),  
after being washed with hexane to remove the oil, was stirred in 70 ml  
of dry dimethylsulfoxide and heated to 65-68° under argon for 1 hour.  
At this point a greenish clear solution resulted. The heating source  
was removed and 75 ml of dried tetrahydrofuran was then added. The  
30      resulting solution was cooled to 5° by means of a methanol-ice bath,

1 and 19 g (93 mmoles) of trimethylsulfonium iodide in 100 ml dry dimethylsulfoxide was added in about 5 minutes. The reaction mixture was stirred for another 5 minutes after complete addition.

5 A solution of 10.4 grams (93 mmoles) of 2-thiophenecarboxaldehyde in 120 ml of tetrahydrofuran was added to a moderate rate while keeping the reaction mixture at 0° to -5°. The mixture was stirred for another 5 minutes after complete addition and at room temperature for 1 hour, the mixture was diluted with 500 ml of ice water and extracted four times with ether. The combined extracts were washed  
10 with saturated brine solution and dried. Removal of the drying agent and solvent gave 10.1 of crude 2-epoxyethylthiophene (yellowish liquid), which was distilled under vacuum to give 8.1 g (69%) of light yellow liquid (b.p. 0.15 mm, 43-5°).

A mixture of 11.6 g (64 mmoles) of homoveratrylamine and  
15 8.1 g (64 mmoles) of 2-epoxyethylthiophene was heated with stirring and under argon at 100° overnight. The reaction mixture was cooled to room temperature and was chromatographed in a silica column (700 g) and eluted with benzene-ethyl acetate gradient. The desired product and its isomer were thus separated. After recrystallization  
20 from ethyl acetate/hexane, 3.6 g (18.4%) of pure N-(8-hydroxy-8-2-thienyl) ethyl homoveratrylamine was obtained (m.p. 102°).



Calculated: 62.51% C; 6.89% H; 4.56% N

Found: 62.36% C; 6.69% H; 4.51% N

25 3.6 Grams (11.8 mmoles) of N-(8-hydroxy-8-2-thienyl)-ethylhomoveratrylamine was dissolved in a mixture of 36 ml of acetic acid and 18 ml of conc. hydrochloric acid. The resulting solution was heated at reflux for 3 hours. The reaction mixture was evaporated under reduced pressure to a brown residue which was then suspended in  
30 5% sodium carbonate solution and thoroughly extracted with ethyl acetate.

1 The extracts were combined, washed once with saturated brine, and dried. Removal of the drying agent and solvent gave 3.3 g of a thick oily residue (96% yield); 1-(2'-thienyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine.

5 The procedure outlined above is the basic method for preparing the compounds of this invention. Others may be prepared by substituting equivalent amounts of the appropriate heterocyclic carboxaldehyde or ethyleneoxide for the 2'-thienyl reactants in the reactions detailed.

10 This compound is also prepared by treatment of 8.9 g (40 mmoles) of 1-hydroxy-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine with 5 ml of thiophene in 45 ml of trifluoroacetic acid under argon at room temperature overnight. After stripping off the volatiles, the residue was dissolved in 250 ml 3N hydrochloric acid. 15 This acidic solution was thoroughly washed with ether, basified with conc. ammonium, extracted 3 times with ethyl acetate. The extracts were combined, washed once with saturated brine and dried anhydrous potassium carbonate. Removal of drying agent and solvent gave 9.2 of the desired base as an oily residue (81%).

20 A sample of this oily residue was dissolved in ethyl ether and ethereal hydrogen bromide was added. An off-white precipitate was obtained. This was recrystallized from methanol-ethyl acetate to give the pure hydrobromide (m.p. 215°).



25 Calculated: 51.90% C, 5.44% H, 3.78% N

Found: 52.10% C; 5.58% H; 3.65% N

1

EXAMPLE 2

3.5 Grams (12 mmoles) of 1-(2'-thienyl)-7,8-dimethoxy-  
 2,3,4,5-tetrahydro-1H-3-benzazepine dissolved in 60 ml of methylene  
 chloride was cooled to -12° by means of a methanol-ice bath, and  
 5 6 ml (62 mmoles) boron tribromide was added dropwise. The resulting  
 solution was stirred at room temperature for 1.5 hours and was then  
 evaporated to a brown residue under reduced pressure. The residue  
 was cooled in ice and treated slowly with methanol. The methanol  
 was evaporated at room temperature under reduced pressure. The  
 10 residue was treated with methanol again and stripped under reduced  
 pressure in a 50° hot-water bath. This treatment was repeated 3  
 times. The final residue was either chromatographed on a silica  
 column eluted with 9:1 chloroform/methanol or dissolved in water,  
 any undissolved material filtered off and the aqueous filtrate  
 15 lyophilized to give pure 1-(2'-thienyl)-7,8-dihydroxy-2,3,4,5-  
 tetrahydro-3-1H-benzazepine hydrobromide salt, m.p. 239-40° (dec),  
 ca. 70% yield.



Calculated: 49.13% C; 4.71% H; 4.09% N; 9.37% S  
 20 Found: 48.91% C; 4.59% H; 4.10% N; 9.10% S

The free base is obtained by dissolving the salt in a  
 minimum amount of water and slowly adding 5% sodium bicarbonate  
 solution until the base separates.

EXAMPLE 3

25 3-Thiophenecarbaldehyde was prepared by following a  
 literature procedure (Org. Syn. Coll. Vol. IV pp. 918-9) from  
 3-thenyl bromide which in turn was prepared also by following a  
 literature procedure (Org. Syn. Coll. Vol. IV, pp 921-3) from  
 3-methylthiophene.

30



1 11.7 Grams (0.28 mole) of sodium hydride (57% of mineral  
oil dispersion having been washed with hexane to remove the oil)  
was stirred in dry dimethylsulfoxide (196 ml) at 60-65° for 2 hours  
under argon. The mixture was diluted with dry tetrahydrofuran  
5 (196 ml), cooled to -5° and trimethylsulfonium iodide (57.12 g,  
0.28 moles) in 196 ml of dry dimethylsulfoxide was added at such a  
rate that the temperature of the reaction mixture did not exceed  
0°. After stirring for another minute after complete addition,  
10 3-thiophenecarboxaldehyde (13.4 g, 0.12 moles) in 84 ml of  
tetrahydrofuran was added. The methanol/ice bath was removed and  
the reaction mixture was allowed to warm to room temperature for  
1.5 hours, then diluted with 1.1 of ice water and extracted thoroughly  
with ether. The extracts were combined, washed with saturated sodium  
chloride solution and dried with anhydrous sodium sulfate. Removal  
15 of the drying agent and solvent gave 16.5 g crude 3-epoxyethylthiophene.  
Since spectral data (ir, nmr) were satisfactory the epoxide was used  
without further purification.

A mixture of 39.8 g (0.22 moles) of homoveratrylamine and  
24.8 g (0.195 moles) of 3-epoxyethylthiophene was heated with  
20 stirring at 100° overnight. The reaction mixture was cooled to room  
temperature and stirred with 5% ethyl acetate in petroleum ether.  
The solution was decanted and the crystals were washed twice more  
with the same solvent mixture to give N-(β-hydroxy-β-3'-thienyl)  
ethylhomoveratrylamine. After recrystallization from ethyl acetate,  
25 21.5 g of pure product was obtained, m.p. 113-4° (36% yield).



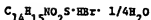
Calculated: 62.51% C; 6.89% H; 4.56% N

Found: 61.87% C; 6.92% H; 4.65% N

1 9.2 Grams (30 mmoles) N-(8-hydroxy-8-3-thienyl)-  
ethylhomoveratrylamine was dissolved in 92 ml of acetic acid and  
46 ml of conc. hydrochloric acid. The mixture was heated at reflux  
for 3 hours, stripped under reduced pressure to a brown residue,  
5 which was then treated with 5% carbonate solution and thoroughly  
extracted with ethyl acetate. The organic extracts were combined  
and washed twice with brine and dried over anhydrous sodium  
sulfate. Removal of drying agent and solvent gave 8.7 g of thick  
oily residue (99% yield), 1-(3'-thienyl)-7,8-dimethoxy-2,3,4,5-  
10 tetrahydro-1H-3-benzazepine.

A sample of this free base was dissolved in methanol and  
ethereal hydrogen chloride was added until acidic. This acidic  
solution was evaporated to dryness. Recrystallization of the  
residue from methanol-ethyl acetate gave the pure hydrochloride  
15 salt (m.p. 178°).

5.25 Grams (18 mmoles) of 1-(3'-thienyl)-7,8-dimethoxy-  
2,3,4,5-tetrahydro-3-lH-benzazepine dissolved in 90 ml of methylene  
chloride was cooled to -12° by means of a methanol/ice bath and  
9 ml of boron tribromide (93 mmoles) was added dropwise. The  
resulting solution was allowed to warm to room temperature for  
20 1.5 hours. The solvent was stripped off to give a brown residue  
which was chilled and carefully treated with methanol. The  
methanol was evaporated under reduced pressure and the resulting  
residue was again treated with methanol and stripped at 50°. This  
process was repeated 3 times and 4.2 g of crude 1-(3'-thienyl)-7,  
25 8-dihydroxy-2,3,4,5-tetrahydro-3-lH-benzazepine hydrobromide was  
obtained. This was further purified by chromatography over silica,  
eluted with 9:1 chloroform:methanol, and dissolved in water,  
charcoaled, and filtered. Lyophilization of the filtrate gave 2.8 g  
of buff colored amorphous powder (m.p. 254-6° dec.).



Calculated: 46.10% C; 5.11% H; 3.84% N; 8.73% S

Found: 45.84% C; 4.89% H; 3.68% N; 8.39% S

#### EXAMPLE 4

To 181 g (1 mole) of homoveratrylamine in 1 l. of ethanol was added 117 g (1.1 mole) of benzaldehyde. The mixture was stirred at room temperature for 15 minutes. A solution of 100 g of potassium borohydride in 500 ml cold water was then slowly added while the solution was kept at near room temperature by external cooling. After complete addition of the hydride solution, the reaction mixture was stirred for 5 hours and then chilled and acidified with 6N hydrochloric acid. Further chilling to 0° precipitated the N-benzyl homoveratrylamine hydrochloride salt which was collected by filtration. The crude product recrystallized from ethanol (m.p. 204-6°).

44 Grams (0.143 moles) of the N-benzylhomoveratrylamine hydrochloride salt was suspended in 440 ml of dry dimethylformamide. To this were added 100 g (0.725 moles) of powdered anhydrous potassium carbonate and 29 g (0.17 mole) of bromoacetaldehyde dimethyl acetal. The reaction mixture was heated at reflux with stirring for 20-24 hours under argon. The salts were then removed by filtration, and the filtrate was evaporated under reduced pressure to yield a dark brown oil. This was dissolved in a water-ethyl acetate mixture and the layers were separated. The water layer was thoroughly extracted with ethyl acetate. The combined organic layers were back washed once with brine solution, dried, and the solvent evaporated to give 46 g of crude product (brown syrup 90% yield). Chromatography gave a 64% yield of pure N-benzyl-N-(β-3,4-dimethoxyphenyl)ethylamino-acetaldehyde dimethyl acetal.

1           The dimethyl acetal (24 g) was dissolved in 240 ml of  
       conc. HCl:HOAc:H<sub>2</sub>O (3:2:1 ratio) and allowed to stand overnight at  
       room temperature. It was then poured into 1 l. ice-water, basified  
       to pH = 8 by addition of conc. ammonia, and extracted with ethyl  
 5       acetate. The extracts were combined, back washed once with  
       saturated brine and dried over anhydrous sodium sulfate. Removal  
       of the drying agent and solvent gave 19.5 g of crude product  
       (92% yield).

10           Chromatography over a silica column gave pure N-benzyl-  
       1-hydroxy-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine in a  
       51% yield. The oily product could be crystallized from ethyl  
       acetate-hexane.

      The "dimethylacetal" reaction described in detail above  
       is another general method which may be used to prepare various  
 15       1-hydroxybenzazepine intermediates of this invention using as starting  
       materials various substituted N-lower alkyl or phenalkylhomoveratry-  
       lamines especially the N-methyl, N-benzyl or N-phenethylhomoveratry-  
       lamines. The reaction apparently does not go on the N-H amines.  
       The N-benzyl compounds are of most general use because the protective  
 20       benzyl group can be readily removed as described hereafter.

      1.1 Grams of the pure N-benzyl-1-hydroxyl benzazepine was  
       dissolved in 50 ml methanol and 220 mg 10% palladium on charcoal  
       wetted with butanol was added. The solution was shaken for 4 hours  
       under hydrogen at 40 psi. The catalyst was removed by filtration and  
 25       the filtrate was evaporated under reduced pressure to give a slightly  
       yellow syrup which was crystallized from ethyl acetate. Recrystalli-  
       zation from acetonitrile (m.p. 153-4°) gave pure 1-hydroxy-7,8-  
       dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine a key new intermediate.

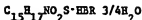
30

1 8.9 Grams (40  $\mu$ moles) of 1-hydroxy-7,8-dimethoxy-  
 2,3,4,5-tetrahydro-1H-3-benzazepine and 2.5 ml of 2-methyl-thiophene  
 were dissolved in 45 ml trifluoroacetic acid. The reaction mixture  
 was allowed to stand at room temperature overnight, then evaporated  
 5 under reduced pressure to an oily residue which was dissolved in  
 250 ml of 3N hydrochloric acid. The acidic solution was thoroughly  
 washed with ether, then basified with conc. ammonia, and finally  
 extracted with ethyl acetate. The organic extracts were combined,  
 washed with saturated brine, and dried over anhydrous sodium sulfate.  
 10 Removal of drying agent and solvent gave 10.1 g. of 1-(5'-methyl-  
 2'-thienyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine as an  
 oil (83.3%); m.p. (HCl) 227-228°. In the same way 1-(2'-  
 thienyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine,  
 and 1-(2'-furyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-  
 15 benzazepine are made using thiophene, 2-bromothiophene and furan.

#### EXAMPLE 5

4.6 Grams (15  $\mu$ moles) of 1-(5'-methyl-2'-thienyl)-  
 7,8-dimethoxy-2,3,4,5-tetrahydro-3H-benzazepine was dissolved in  
 45 ml methylene chloride under argon; the solution was cooled to  
 -12° by a methanol-ice bath, and 78 ml of boron tribromide in  
 20 methylene chloride (1 g/5 ml) was slowly added. The dark brown  
 solution which resulted was allowed to warm to room temperature  
 for one hour, and evaporated under reduced pressure to a brown  
 residue. This was chilled to 0°, methanol was slowly added and  
 then evaporated. This was repeated 5 times and the resulting dark  
 25 brown gum was dissolved in water and filtered through a pad of  
 "Supercel". The filtrate was lyophilized to give a yellowish  
 powder which was further purified by chromatography on silica gel.  
 Elution with 9:1 chloroform:methanol gave 2.4 g of pure 1-(5'-methyl-  
 2'-thienyl)-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine  
 30

1 hydrobromide (m.p. 169° dec.).



Calculated: 48.72% C; 4.91% H; 3.78% N

Found: 48.86% C; 4.84% H; 3.87% N

5 In similar manner the 7,8-dihydroxy-1-(2'-thienyl), (5'-bromo-2'-thienyl) and (2'-furyl) congeners are made from the 7,8-dimethoxy compounds of Example 4.

#### EXAMPLE 6

10 A mixture of 10.2 g (0.056 mole) of homoveratrylamine and 5.9 g (0.053 mole) of 2-epoxyethylfuran were mixed and heated on the steam bath overnight and worked up as in Example 1 to give N-(β-hydroxy-8-2'-furyl)ethylhomoveratrylamine, as a crystalline solid which was recrystallized from ethyl acetate-petroleum ether (m.p. 90°).

15 The furylaminolcohol (2.9 g) was cyclized in 30 ml of trifluoroacetic acid at room temperature overnight. The black mixture was poured into 20 ml of ammonium hydroxide/300 ml of ice and 40 ml of ethyl acetate, and more ammonia was added to pH 9. The combined organic layer and subsequent extracts were washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo  
20 after removal of the drying agent gave 2.51 g of oily product, 1-(2'-furyl)-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine. This material is identical to the same product prepared by catalytic hydrogenation of the N-benzyl derivative (Examples 7 and 8) using palladium on charcoal in methanol at 50°.

#### EXAMPLE 7

25 A solution of 20.1 g (64 mmole) of 1-hydroxy-N-benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine in 130 ml of methylene chloride was treated with 14 g (0.2 mole) of furan and 16 ml of ethereal boron trifluoride. After standing overnight at  
30 room temperature the reaction mixture was stirred with concentrated

- 1 ammonium hydroxide and ice. The methylene chloride phase was separated and extracted with 1M phosphoric acid. The acid extracts were neutralized and extracted with ethyl acetate. The dried extracts were evaporated to 19.8 g of crude product [1-(2'-furyl)-3-benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine] which was purified by chromatography over silica.

EXAMPLE 8

- The N-benzyl product (14.2 g, 0.12 mole), prepared as in Example 7, in methylene chloride was reacted with 145 ml of boron tribromide-methylene chloride (1 g/5 ml) at room temperature for 1.25 hours. The desired 1-(2'-furyl)-3-benzyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine was isolated as described above. This compound was debenzylated by hydrogenolysis as described in Example 6 to give 1-(2'-furyl)-3-benzyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine as described above. This compound was debenzylated by hydrogenolysis as described in Example 6 to give 1-(2'-furyl)-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine. Its hemi-fumarate salt was prepared in methanol and was recrystallized from water (m.p. 267° dec.).

- 20  $C_{14}H_{15}NO_3 \cdot 1/2C_4H_4O_4 \cdot 1/4H_2O$   
 Calculated: 62.43% C; 5.73% H; 4.56% N  
 Found: 62.78% C; 6.14% H; 4.52% N

EXAMPLE 9

- 25 Three solutions each with 0.31 g (1 mmole) of 1-hydroxy-3-benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine in 2 ml of methylene chloride containing boron trifluoride etherate were respectively reacted with an excess of furan, 2-methylfuran and 2-cyanomethylfuran at room temperature overnight. Each was quenched in ammonia solution, isolated and passed over silica gel. This layer chromatography on silica gel using cyclohexane-ethyl acetate (7:3)
- 30

1 gave  $R_f$  values of 0.68, 0.70 and 0.43 respectively with the starting material at 0.14. These are the 2'-furyl, 5'-methyl-2'-furyl and 5'-cyanomethyl-2'-furyl congeners which can be optionally debenzylated and demethylated as described to give 1-(2'-furyl)-7,8-dihydroxy-  
 5 2,3,4,5-tetrahydro-1H-3-benzazepine, its methylfuryl and its cyanomethylfuryl congeners.

Repeating this reaction with 1-hydroxy-3-methyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine (prepared from N-methylhomoveratrylamine as in Example 4 and 2-methylthiophene  
 10 gives 1-(5'-methyl-2'-thienyl)-3-methyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine. Demethylation as described above gives 1-(5'-methyl-2'-thienyl)-3-methyl-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide.

#### EXAMPLE 10

15 A mixture of 7.9 g (25.2 mmoles) of 1-hydroxy-3-benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine, 6.35 g (50.4 mmoles) of methyl furoate and 6.2 ml (50.4 mmoles) of boron trifluoride etherate was reacted at room temperature for 1.5 hours. Another 3.1 ml of trifluoride was added followed by standing at room temperature overnight.  
 20 The product, 1-(5'-carbomethoxy-2'-furyl)-benzyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine was isolated and purified by methods similar to those of the previous examples. This material was demethylated to the 7,8-dihydroxy compound and debenzylated as described above to give 1-(5'-carbomethoxy-2'-furyl)-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine hemifumarate hydrate, m.p. 198-200° (dec.).  
 25

#### EXAMPLE 11

Reacting 2-chloro-3,4-dimethoxyphenylethylamine, 2-fluoro-3,4-dimethoxyphenylethylamine or 2-trifluoromethyl-3,4-dimethoxyphenylethylamine (prepared via 2-trifluoromethyl-3,4-dimethoxytoluene) in a  
 30 stoichiometric quantities with 2-epoxyethylthiophene as in Example 1



gives 2-chloro-1-(2'-thienyl)-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine, 6-fluoro-1-(2'-thienyl)-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine and 6-trifluoromethyl-1-(2'-thienyl)-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-3-benzazepine via their 7,8-dimethyl ethers.

#### EXAMPLE 12

A mixture of 4.5 g of 6-chloro-7,8-dimethoxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine, 0.02 ml of *n*-butyl bromide and 0.02 mol of potassium hydroxide is dissolved in 120 ml of dry methanol and refluxed for 48 hours. The reaction mixture is evaporated to dryness, taken up in ethyl acetate and filtered to remove inorganic salts. The filtrate is washed with water, dried and evaporated to give 3-*n*-butyl-6-chloro-7,8-dimethoxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine.

The 3-*n*-butyl benzazepine (0.01 mol) is dissolved in 120 ml of dry methylene chloride and 0.032 mol of boron tribromide is added dropwise at -10°. The solution is warmed to room temperature and stirred for two hours. The excess boron tribromide is destroyed with methanol added dropwise with ice-cooling. The cold solution is refluxed on the steam bath to remove hydrogen bromide and evaporated. The residue is treated with brine at reflux for 2 hours to yield 3-*n*-butyl-6-chloro-7,8-dihydroxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide.

Using N-alkylation procedures described above but using 7,8-dimethoxy-1-(5'-methyl-2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine as a model compound the *N*-allyl, *N*-phenethyl, *N*-butyl, *N*-amyl or *N*-2,2-dimethylallyl derivatives are prepared. Hydrolysis of the methoxy groups as described gives the active 7,8-dihydroxy compounds.

#### EXAMPLE 13

A 3.9 g sample of 7,8-dihydroxy-1-(3'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine is slurried in 25 ml of acetone and

1 (0.016 mol, 10% excess) of ethylene oxide is added. The mixture is placed in a pressure bottle and stirred at ambient temperature for about 40 hours. The reaction mixture is then heated to 60-80° for 30 minutes, cooled and filtered. Concentration of the filtrate gives  
 5 a solid which is taken up in ethyl acetate and reprecipitated with ether. The solid thus obtained is dissolved in ethanol and treated with ethereal hydrogen chloride to give 7,8-dihydroxy-3-(2-hydroxy-ethyl)-1-(3'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride.

#### EXAMPLE 14

10 A 4.0 g sample of 3-benzyl-7,8-dihydroxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (prepared from the 3-unsubstituted benzazepine by reaction with benzyl bromide in the presence of potassium carbonate) is dissolved in 50 ml of acetic anhydride and the solution is heated on a steam bath for one hour. The reaction mixture is cooled,  
 15 ice-water is added and the solution is evaporated to dryness. The residue is triturated with ethyl acetate, the solution washed with water, dried and the solvent removed in vacuo to leave an oil. The latter is dissolved in ether and ethereal hydrogen chloride is added to precipitate 3-benzyl-7,8-diacetoxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride.

20 7,8-dihydroxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (10 g) is dissolved in trifluoroacetic acid and reacted with a stoichiometric amount of acetyl bromide at room temperature for 1-2 hours. The reaction mixture is evaporated and the residue is triturated in ether-1-propanol to give the desired  
 25 diacetoxy derivative.

Substituting other alkanoyl anhydrides or chlorides gives various 7,8-alkanoyl derivatives such as the diacetoxy derivatives of 2'-furyl, 5'-methyl-2'-furyl, 5'-cyanomethyl, 3'-thienyl, 5'-methyl-2'-thienyl, and 5'-bromo-2'-thienyl compounds.

30

1090757

EXAMPLE 15

1 7,8-Dihydroxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (5 g) is suspended in 500 cc of benzene. Trifluoroacetic anhydride (15 g) is added dropwise rapidly. The solution is stirred  
5 an additional hour and the volatiles stripped off, leaving the N,O,O-tris-trifluoroacetyl derivative. This is added directly to 500 cc of methanol and hydrogen chloride gas bubbled in for a few minutes. The reaction is stirred for 2 hours and then the solvent stripped off, leaving 7,8-dihydroxy-1-(2'-thienyl)-3-trifluoroacetyl-2,3,4,5-tetra-  
10 hydro-1H-3-benzazepine.

EXAMPLE 16

Dry dimethylformamide (50 ml) is deoxygenated four times by pulling a vacuum and refilling the vacuated flask with argon. 7,8-Dihydroxy-1-(2'-thienyl)-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine (5 g) is added and dissolved as the solution is deoxygenated  
15 once more. Methylene bromide (5.3 g) potassium carbonate (5 g) and cupric oxide (0.13 g) are added and the solution is deoxygenated a final time. The reaction is heated at 150° under argon for 2 hours.

It is worked up by pouring into 2 l. of ice water while stirring. The aqueous suspension is extracted four times with 300-400  
20 cc ether, and the ether is back extracted three times with 1.5 l. water. The ether is dried and evaporated. The residue is dissolved in chloroform and chromatographed on silica gel to give 7,8-methylenedioxy-1-(2'-thienyl)-3-trifluoroacetyl-2,3,4,5-tetrahydro-1H-3-benzazepine.

EXAMPLE 17

25 A suspension of 7,8-dihydroxy-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide (3.4 g) in methanol (40 ml) is reacted with 2.5 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in methanol at 0° for 1 hour. The 1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-dione hydrobromide was collected by filtration and  
30 washed with ether. The dione hydrobromide salt is added to an excess

- 1 of methyl mercaptan in methanol. After 1 hour the solution is  
 evaporated to give a residue of the 6-methylthio and 9-methylthio  
 isomers. Separation over a silica gel column gives 6-methylthio-1-  
 (2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide salt.  
 5 Similarly 6-methylthio-3'-thienyl and 2'-furyl congeners  
 are made.

EXAMPLE 18

- 5.5 Grams (18 mm) of 7,8-dimethoxy-1-(5'-methyl-2'-thienyl)-  
 2,3,4,5-tetrahydro-1H-3-benzazepine was dissolved in 120 ml of ethyl-  
 10 formate and was heated at reflux for 24 hours. After addition of 50 ml  
 of ethyl ether, the reaction mixture was washed with 3 x 30 ml of 3N  
 hydrochloric acid, 2 x 20 ml of 5% sodium bicarbonate, and then brine.  
 After drying over sodium sulfate and removal of the drying agent, the  
 solvent was evaporated to give 4.8 g of the oily N-formyl derivative.

EXAMPLE 19

- 15 To 120 ml of ethyl ether under argon, 2.15 g of lithium aluminum  
 hydride was added followed by addition of 4.7 g (14.2 mmoles) of the  
 N-formyl derivative in 80 ml of benzene. The resulting suspension was  
 gently refluxed for 5 hours. It was then cooled and the excess hydride  
 20 was decomposed by addition of 6 ml of methanol in 25 ml ether, 2.15 ml of  
 water, 2.15 ml of 10% alkali, and 6.45 ml of water, in that sequence.  
 The solid formed was removed by filtration. The filtrate was evaporated  
 to an oil which was taken up in ethyl acetate and thoroughly extracted with  
 3N hydrochloric acid. The acidic extracts were combined, washed with ether,  
 25 basified to pH 8, and thoroughly extracted with ethyl acetate. The organic  
 extracts were combined and dried over anhydrous sodium carbonate. Removal  
 of the drying agent and solvent gave 3.6 g of 1-(5'-methyl-2'-thienyl)-3-  
 methyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1H-3-benzazepine.

0 This was dissolved in methanol and ethereal hydrogen chloride  
 was added. The solution was stripped to dryness under reduced pressure to  
 give 7,8-dimethoxy-1-(5'-methyl-2'-thienyl)-3-methyl-2,3,4,5-tetrahydro-

- 1 1H-3-benzazepine which was recrystallized from methanol-ethyl acetate hydrochloride (m.p. 227-8°).

- Substituting the 1-(2'-thienyl), 1-(3'-thienyl) or 1-(2'-furyl) congeners in the procedures of Examples 19-20 with obvious variations gives
- 5 7,8-dimethoxy-1-(2'-thienyl)-3-methyl-3,4,5-tetrahydro-1H-3-benzazepine hydrochloride, 7,8-dimethoxy-1-(3'-thienyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride or 7,8-dimethoxy-1-(2'-furyl)-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hemifumarate. Splitting the ethers as described above gives the three dihydroxy congeners.

10 EXAMPLE 20

- Treatment of the dione hydrobromide salt with anhydrous hydrogen bromide in methylene chloride or with diluted hydrobromic acid, gives 6-bromo-1-(2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide salt. Similarly the 6-bromo-1-(5'-methyl-2'-thienyl), 6-bromo-1-(2'-furyl), 6-bromo-3'-thienyl analogs are prepared.

<u>Ingredients</u>	<u>Mg. per Capsule</u>
7,8-Dihydroxy-1-(5'-methyl-2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as an acid addition salt)	125 (free base)
Magnesium stearate	2
Lactose	200

- 20 The above ingredients are thoroughly mixed and placed into hard gelatin capsules. Such capsules are administered orally to subjects in need of treatment from 1-5 times daily to induce dopaminergic activity.

25

30

EXAMPLE 21

<u>Ingredients</u>	<u>Mg. per Tablet</u>
7,8-Dihydroxy-1-(2'-thianyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (as an acid addition salt)	200 (free base)
Corn starch	30
Polyvinyl pyrrolidone	12
Corn starch	16
Magnesium stearate	3

The first two ingredients are thoroughly mixed and granulated. The granules obtained are dried, mixed with the remaining corn starch and magnesium stearate, and compressed into tablets.

The capsules or tablets thusly prepared are administered orally to an animal or human, requiring stimulation of either peripheral or central dopamine receptors to induce hypotension or to treat the symptoms of Parkinson's disease within the dose ranges set forth hereinabove. Similarly other compounds of Formula I and the illustrative examples can be formulated in the same manner to give pharmaceutical compositions useful in the methods of this invention based on the chemical characteristics and relative biological activity using the test methods outlined.

A subgeneric group of compounds within the illustrative generic group of Formula I are those in which:

R is phenethyl, benzyl, lower alkyl of 1-5 carbon atoms, hydroxyethyl or lower alkenyl of 3-5 carbon atoms;

R<sub>1</sub> is hydrogen, halo, trifluoromethyl, lower alkylthio, trifluoromethylthio, methyl or methoxy;

R<sub>2</sub> and R<sub>3</sub> are each hydrogen, lower alkyl of 1-5 carbon atoms, lower alkanoyl of 2-5 carbon atoms or, when taken together, methylene or ethylene;

R<sub>4</sub> is hydrogen, halo or methyl; and

X is -O- or -S-.

1 In this subgeneric group, particular compounds are those in  
which R is methyl or allyl; R<sub>1</sub> is hydrogen, chloro, bromo or  
methylthio; R<sub>2</sub> and R<sub>3</sub> are the same and are hydrogen, methyl  
or acetyl; R<sub>4</sub> is hydrogen or 5'-methyl; and X is -S-.

5 The compounds of the above subgeneric group have  
particularly useful hypotensive activity, producing arterial  
hypotension and concomitant bradycardia. This activity is  
demonstrated in anesthetized spontaneously hypertensive rats  
(SHR). In this pharmacological procedure, adult male SHR,  
10 weighing approximately 350-400 grams, are anesthetized with  
pentobarbital sodium (65 mg/kg, i.p.). The trachea is cannu-  
lated and the rats are allowed to respire spontaneously.  
Pulsatile arterial blood pressure is measured from a cannulated  
carotid artery using a Statham transducer (P23AA). Mean  
arterial blood pressure is calculated as diastolic blood  
15 pressure plus 1/3 pulse pressure. Cardiac rate is monitored  
by means of a cardiometer triggered by the systolic  
blood pressure pulse. Phasic arterial blood pressure and  
cardiac rate are recorded using a multichannel oscillograph.  
Drug solutions are administered through a cannulated tail  
20 vain. Approximately 10 minutes are allowed to elapse,  
following surgery, for equilibration of the preparation.  
After the equilibration period, a control tracing of the  
directly measure parameters is taken. Each rat then receives  
an initial dose of 1 mcg/kg of a test compound. Arterial  
25 blood pressure and cardiac rate responses are recorded and  
expressed as absolute change from the respective control  
value established immediately prior to the injection. This  
sequence is repeated at approximately 5-10 minute intervals,  
with increasing dose levels of the test compound, until each  
30 rat has received individual doses of 1, 3, 10, 30, 100, 300  
and 1000 mcg/kg.

The following table sets forth mean arterial blood pressure and cardiac rate responses produced in the anesthetized SHR, according to the above described procedure, upon i.v. administration to 3 rats of 7,8-dimethoxy-3-methyl-1-(5'-methyl-2'-thienyl)-2,3,4,5-tetrahydro-1H-3-benzazepine as its hydrochloride salt (doses refer to mcg/kg of the free base).

Change in Mean Arterial Blood Pressure (mmHg)

1 mcg/kg	3 mcg/kg	10 mcg/kg	30 mcg/kg	100 mcg/kg	300 mcg/kg	1000 mcg/kg
+5.6±1.3	+10.0±1.1	+7.3±1.7	-21.6±11.3	-88.0±7.9	-75.0±7.2	-67.2±4.4

Change in Cardiac Rate (beats/minute)

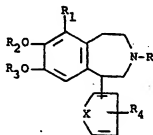
1 mcg/kg	3 mcg/kg	10 mcg/kg	30 mcg/kg	100 mcg/kg	300 mcg/kg	1000 mcg/kg
-4.6±1.7	-1.0±1.5	-0.6±2.8	-73.6±25.4	-174±29.7	-144±30.8	-98±25.2

This compound therefore produced average maximum changes in arterial blood pressure of -88 mmHg and cardiac rate of -174 beats/minute with dose-related hypotension from 30-1000 mcg/kg and bradycardia over the entire dose range.



The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. The method of preparing a compound of the formula:



Formula I

in which:

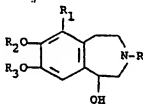
R is hydrogen, benzyl, phenethyl, lower alkanoyl of 1-5 carbons, lower alkyl of 1-5 carbons, hydroxyethyl or lower alkenyl of 3-5 carbons;

R<sub>1</sub> is hydrogen, halo, trifluoromethyl, methylthio, trifluoromethylthio, methyl or methoxy;

R<sub>2</sub> and R<sub>3</sub> are each hydrogen, lower alkyl of 1-5 carbons, lower alkanoyl of 2-5 carbons or, when taken together, methylene or ethylene;

R<sub>4</sub> is hydrogen, halo, cyanomethyl, methyl or carbomethoxy; and

X is -O- or -S- ;  
or the pharmaceutically acceptable nontoxic salts thereof,  
comprising reacting a compound of the formula:

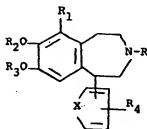


in which R is lower alkyl, benzyl or phenethyl,  $R_1$  is hydrogen, halo, trifluoromethyl, methylthio, trifluoromethylthio, methyl or methoxy; and  $R_2$  and  $R_3$  are lower alkyl, and, when taken together, methylene or ethylene; with a compound of the formula:



in which  $R_4$  is hydrogen, halo, methyl, cyanomethyl or carbomethoxy in the presence of at least one equivalent of an acid catalyst; followed by optional N-alkylation of a compound of Formula I in which R is hydrogen to give a compound in which R is benzyl, phenethyl, lower alkyl, hydroxy ethyl or lower alkenyl and optional O-dealkylation of a compound of Formula I in which  $R_2$  and  $R_3$  are alkyl or, when taken together, methylene or ethylene to give a compound of Formula I in which  $R_2$  and  $R_3$  are hydrogen and then optional salt formation by reacting a base of Formula I with an inorganic or organic acid.

2. The method of claim 1 in which R is methyl, and X is -S-.
3. The method of claim 1 in which R is methyl,  $R_1$  is hydrogen,  $R_2$  and  $R_3$  are methyl,  $R_4$  is 5'-methyl, X is -S- and the thienyl ring is attached at position 2'.
4. The method of claim 3 in which a nontoxic salt is formed.
5. The method of claim 4 in which the hydrochloride or methanesulfonate salt is formed.
6. A compound of the formula:



1 in which:

R is hydrogen, benzyl, phenethyl, lower alkanoyl of 1-5 carbons, lower alkyl of 1-5 carbons, hydroxyethyl or lower alkenyl of 3-5 carbons;

5  $R_1$  is hydrogen, halo, trifluoromethyl, methylthio, trifluoromethylthio, methyl or methoxy;

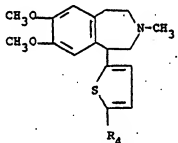
$R_2$  and  $R_3$  are each hydrogen, lower alkyl of 1-5 carbons, lower alkanoyl of 2-5 carbons or, when taken together, methylene or ethylene;

10  $R_4$  is hydrogen, halo, cyanomethyl, methyl or carbomethoxy and

X is -O- or -S-;

or the pharmaceutically acceptable nontoxic salts thereof when prepared by the method of claim 1 or by their obvious chemical equivalents.

15 7. A compound of the formula:



20 in which  $R_4$  is methyl as the base or as the hydrochloride or methanesulfonate when prepared by the method of claim 3 or by their obvious chemical equivalents.

25

30

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**